**BACKGROUND**

An anti-human CD33 monoclonal murine antibody (My9-24.7 mg/kg Ab; 475 mcg/kg DGN462) was selected and humanized by IMGN779 (5 µg/kg DGN462; days 1, 4) or with formulation buffer, followed by the addition of MST 28. After 2-8 of MST 28, no signs of toxicity were observed above 450 mg/kg was determined.

Payloads were evaluated in vivo for toxicity on human AML cell lines by subcutaneous injection of 72 h with serial dilutions of payload and with formulations followed by the addition of MST 28. After 2-8 of MST 28, no signs of toxicity were determined.

ACD concentrations were evaluated in vivo for single-dose toxicity in rats and mice tolerability in CD33-targeting ADCs. For mouse tolerability, BW was stable and CD 1 mice were exposed to the antibody for 2 weeks, with clinical signs and BW loss were the endpoints for dose-determined models.

ACD concentrations were evaluated in vivo for single-dose toxicity in rats and monkeys. The antitumor activity of IMGN79 was evaluated in AML xenograft models in multiple dose tolerability in CD33-targeting ADCs. For mouse tolerability, BW was stable and CD 1 mice were exposed to the antibody for 2 weeks, with clinical signs and BW loss were the endpoints for dose-determined models.

DGN462 (mono-imine, DNA mono-alkylator) and DGN484 (di-imine, DNA cross-linker) payloads have comparable IC50s as free drugs and as CD33-targeting conjugates.

**DNA mono-alkylating payload (DGN462) is better tolerated than DNA cross-linking payload (DGN484)**

**IMGN779 (Z4681a-s-SPDB-DGN462) at MTD has a consistent toxicity profile across multiple species**

**IMGN779 is highly active against disseminated AML xenografts**

**Cleavable linker formats were better tolerated than non-cleavable linker**

**Additional benefit derived from fractionated IMGN79779 dosing against AML xenografts**

**SUMMARY**

- DNA mono-alkylating payload confers higher MTD, with similar MTD, compared to DNA cross-linking payload, resulting in higher TI in xenograft models.
- Cleavable linker format confers higher MTD than non-cleavable linker.
- IMGN779, designed as a next generation CD33-targeting ADC, utilizes a novel DNA mono-alkylating DGN462 payload and a cleavable disulphide linker, combining components selected to maximize anti-AML activity and preclinical safety.
- IMGN779 is highly active and well-tolerated in preclinical repeat-dosing regimens.
- IMGN779 is highly active in multiple AML xenograft models, including models with poor prognostic factors.
- IMGN779 dose fractionation provides an additional long-term benefit over treating AML xenografts with a single high dose.
- These results provide the foundation for the clinical evaluation of IMGN779 in AML.

Clinical testing is ongoing: NCT02674763: Open-label Study of IMGN79 in Adult Patients With Relapsed/Refractory CD33-positive Acute Myeloid Leukemia. Clinical Poster: P652, Saturday, June 24; 17:30 to 19:00, Hall 7

**P526**

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**DESIGNING THE NEXT GENERATION CD33-TARGETING ADC: IMGN779, SELECTED FOR POTENCY, NOVEL MECHANISM AND PRECLINICAL TOLERABILITY, WITH HIGH ACTIVITY IN DISSEMINATED AML MODELS AND MULTI-DOSE REGIMENS**

**ABSTRACT**

Drug development is challenged by the need to develop novel ADCs with improved activity and tolerability. We report CD33 targeting ADCs with improved activity and tolerability compared to currently available ADCs, and highlight the design challenges and findings that enabled the selection of IMGN779 for clinical evaluation.

**RESULTS**

- **DNA mono-alkylating payload (DGN462)** is better tolerated than DNA cross-linking payload (DGN484)
- **Cleavable linker formats** were better tolerated than non-cleavable linker
- **IMGN779 (Z4681a-s-SPDB-DGN462)** at MTD has a consistent toxicity profile across multiple species
- **IMGN779 is highly active against disseminated AML xenografts**
- **Additional benefit derived from fractionated IMGN79779 dosing against AML xenografts**

**CONCLUSIONS**

- IMGN779, a novel DNA mono-alkylating ADC, has superior activity and tolerability compared to currently available ADCs.
- The design and development of IMGN779 demonstrate a successful approach to overcoming the challenges of CD33 targeting ADCs.

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**REFERENCES**


**CONFLICT OF INTEREST**

The authors declare no conflicts of interest.